REMARKS

Claims 1, 2, 8-10, 13-16, 18-22, 27-30, 61, 65, and 68-78 are pending in the present application. Claims 1-2, 8-10, 13-16, 18-22, 27-30, 61, 65, 68-73 stand withdrawn from further consideration as directed to a non-elected invention. Claims 3-7, 11-2, 17, 23-26, 31-60, 62-54 and 66-67 have been cancelled. Claims 74-78 are currently under examination and claims 74-78 are amended herein. The cancellation of claims 3-7, 11-2, 17, 23-26, 31-60, 62-54 and 66-67 and the amendment of claims 74-78 have been effected so as to accelerate prosecution of the instant application. Applicants may pursue claims to additional subject matter in one or more divisional applications. Reconsideration of all pending claims is respectfully requested in view of the amendments made and the following remarks.

The Examiner has rejected claim 78 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner has rejected claim 78 for reciting "nonfibrotic inflammatory response." Applicants have amended claim 78 herein to delete the phrase "nonfibrotic inflammatory response" and to recite "wherein the inflammatory response occurs in the context of aberrant, unwanted or otherwise inappropriate acute inflammation of the airways." Support for this amendment can be found at page 1 in the Abstract of the application as filed. In view of this amendment, Applicants respectfully request that the rejection of claim 78 under 35 U.S.C. §112, first paragraph be withdrawn.

The Examiner has rejected claim 78 under 35 U.S.C. §102(b) as being allegedly anticipated by WO 03/006006057 (hereinafter "the '057 publication"), stating that the '057 publication teaches use of follistatin to treat <u>diseases associated with fibrosis</u> (emphasis in the Examiner's Office Action dated September 26, 2011). Applicants have made amendments to claim 78 herein so that claim 78 is now drawn to a "method of downregulating the inflammatory response in a mammal, … wherein the downregulation is achieved by introducing follistatin into said mammal, and wherein the inflammatory response occurs in the context of aberrant,

unwanted or otherwise inappropriate acute inflammation of the airways." Applicants submit, therefore, that because the '057 publication is directed specifically to treatment of diseases associated with fibrotic disorders and not to acute inflammation, the '057 publication is no longer apposite to claim 78 as amended, and respectfully request that the rejection of the claim under 35 U.S.C. §102(b) as allegedly being anticipated by WO 03/006006057 be withdrawn. Applicants respectfully remind the Examiner that aberrant, unwanted or otherwise inappropriate acute inflammation of the airways--such as in severe acute respiratory distress syndrome--can kill a subject well before fibrosis occurs, if indeed fibrosis occurs at all.

The Examiner has rejected claims 74-75 and 78 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent Publication 2002/0192216 (hereinafter 'the '216 publication) as evidenced by van Eyll et al. The '216 publication discloses that follistatin is an inhibitor of the Hedgehog signaling pathway, and the '216 publication recites asthma, emphysema, and idiopathic interstitial lung disease as a few of many diseases treatable by inhibiting the Hedgehog signaling pathway. The Examiner further has cited *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.* for the proposition that when a claimed process is not directed to a new use, consists of the same steps described in a prior art reference, and the newly-discovered result of a known process is inherent, the process is not patentable. Moreover, the Examiner has cited *In re Wiseman* for the proposition that mere recognition of latent properties does not render nonobvious an otherwise known invention.

As Applicants have argued previously the '216 publication discloses that follistatin is an inhibitor of an intracellular signaling pathway, but fails to provide an enabling disclosure regarding the use of follistatin to treat any therapeutic indication whatsoever. Again, Applicants note that no examples or evidence was presented in the '216 publication relating to the efficacy of follistatin to treat any disease, disorder or condition. Applicants strongly dispute whether the public would have been in possession of any therapeutic treatment given the disclosure in the '216 publication. As argued previously, the '216 publication teaches administration of an inhibitor of the Hedgehog signaling pathway to treat:

> …adult respiratory distress syndrome; chronic obstructive airway disorders/chronic obstructive pulmonary disease including asthma, emphysema and chronic bronchitis; atelectasis; occupational lung disease including silicosis; hypersensitivity diseases of the lung including hypersensitivity pneomonitis; idiopathic interstitial lung diseases

including idiopathic pulmonary fibrosis, usual interstitial pneumonia, desquamative interstitial pneumonia and acute interstitial pneumonia; and pleural fibrosis…. The present invention is also useful in treating immune disorders such as autoimmune diseases or graft rejection such as allograft rejection.

Examples of disorders that may be treated include a group commonly called autoimmune diseases. The spectrum of autoimmune disorders ranges from organ specific diseases (such as thyroiditis, insulitis, multiple sclerosis, iridocyclitis, uveitis, orchitis, hepatitis, Addison's disease, myasthenia gravis) to systemic illnesses such as rheumatoid arthritis or lupus erythematosus. Other disorders include immune hyperreactivity, such as allergic reactions.

In more detail: Organ-specific autoimmune diseases include multiple sclerosis, insulin dependent diabetes mellitus, several forms of anemia (aplastic, hemolytic), autoimmune hepatitis, thyroiditis, insulitis, iridocyclitis, skleritis, uveitis, orchitis, myasthenia gravis, idiopathic thrombocytopenic purpura, inflammatory bowel diseases (Crohn's disease, ulcerative colitis).

Systemic autoimmune diseases include: rheumatoid arthritis, juvenile arthritis, scleroderma and systemic sclerosis, sjogren's syndrom, undifferentiated connective tissue syndrome, antiphospholipid syndrome, different forms of vasculitis (polyarteritis nodosa, allergic granulomatosis and angiitis, Wegner's granulomatosis, Kawasaki disease, hypersensitivity vasculitis, Henoch-Schoenlein purpura, Behcet's Syndrome, Takayasu arteritis, Giant cell arteritis, Thrombangiitis obliterans), lupus erythematosus, polymyalgia rheumatica, essentiell (mixed) cryoglobulinemia, Psoriasis vulgaris and psoriatic arthritis, diffus fasciitis with or without eosinophilia, polymyositis and other idiopathic inflammatory myopathies, relapsing panniculitis, relapsing polychondritis, lymphomatoid granulomatosis, erythema nodosum, ankylosing spondylitis, Reiter's syndrome, different forms of inflammatory dermatitis.

A more extensive list of disorders includes: unwanted immune reactions and inflammation including arthritis, including rheumatoid arthritis, inflammation associated with hypersensitivity, allergic reactions, asthma, systemic lupus erythematosus, collagen diseases and other autoimmune diseases, inflammation associated with atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, vascular inflammatory disorders, respiratory distress syndrome or other cardiopulmonary diseases, inflammation associated with peptic ulcer, ulcerative colitis and other diseases of the gastrointestinal tract, hepatic fibrosis, liver cirrhosis or other hepatic diseases, thyroiditis or other glandular diseases, glomerulonephritis or other renal and urologic diseases, otitis or other oto-rhino-laryngological diseases, dermatitis or other dermal diseases, periodontal diseases or other dental diseases, orchitis or epididimo-orchitis, infertility, orchidal trauma or other immune-related testicular diseases, placental dysfunction, placental insufficiency, habitual abortion, eclampsia, pre-eclampsia and other immune and/or inflammatory-related gynaecological diseases, posterior uveitis,

> intermediate uveitis, anterior uveitis, conjunctivitis, chorioretinitis, uveoretinitis, optic neuritis, intraocular inflammation, e.g. retinitis or cystoid macular oedema, sympathetic ophthalmia, scleritis, retinitis pigmentosa, immune and inflammatory components of degenerative fondus disease, inflammatory components of ocular trauma, ocular inflammation caused by infection, proliferative vitreo-retinopathies, acute ischaemic optic neuropathy, excessive scarring, e.g. following glaucoma filtration operation, immune and/or inflammation reaction against ocular implants and other immune and inflammatory-related ophthalmic diseases, inflammation associated with autoimmune diseases or conditions or disorders where, both in the central nervous system (CNS) or in any other organ, immune and/or inflammation suppression would be beneficial, Parkinson's disease, complication and/or side effects from treatment of Parkinson's disease, AIDS-related dementia complex HIV-related encephalopathy, Devic's disease, Sydenham chorea, Alzheimer's disease and other degenerative diseases, conditions or disorders of the CNS, inflammatory components of stokes, post-polio syndrome, immune and inflammatory components of psychiatric disorders, myelitis, encephalitis, subacute sclerosing pan-encephalitis, encephalomyelitis, acute neuropathy, subacute neuropathy, chronic neuropathy, Guillaim-Barre syndrome, Sydenham chora, myasthenia gravis, pseudo-tumour cerebri, Down's Syndrome, Huntington's disease, amyotrophic lateral sclerosis, inflammatory components of CNS compression or CNS trauma or infections of the CNS, inflammatory components of muscular atrophies and dystrophies, and immune and inflammatory related diseases, conditions or disorders of the central and peripheral nervous systems, post-traumatic inflammation, septic shock, infectious diseases, inflammatory complications or side effects of surgery or organ, inflammatory and/or immune complications and side effects of gene therapy, e.g. due to infection with a viral carrier, or inflammation associated with AIDS, to suppress or inhibit a humoral and/or cellular immune response, to treat or ameliorate monocyte or leukocyte proliferative diseases, e.g. leukaemia, by reducing the amount of monocytes or lymphocytes, for the prevention and/or treatment of graft rejection in cases of transplantation of natural or artificial cells, tissue and organs such as cornea, bone marrow, organs, lenses, pacemakers, natural or artificial skin tissue.
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> The present invention is also useful in cancer therapy, particularly in diseases involving the conversion of epithelial cells to cancer. The present invention is especially useful in relation to adenocarcinomas such as: small cell lung cancer, and cancer of the kidney, uterus, prostrate, bladder, ovary, colon and breast.

‘216 publication at ¶¶149-155. Applicants again contend that the ‘216 publication tosses out the mere germ of an idea relating to inhibiting the Hedgehog signaling pathway—a key regulator of animal development—to treat a panoply of diseases, and that one skilled in the art would have been hard pressed to identify follistatin specifically as one of the many disclosed inhibitors of the Hedgehog signaling pathway as a therapeutic agent without undue experimentation. Dr. David de Kretser so states at ¶ 8 of the Declaration of David Morritz de Kretser (“de Kretser

Declaration") submitted with Applicants' Response filed 08 July 2011. Moreover, in his Declaration Dr. de Kretser concluded that there is a high likelihood that a therapeutic response may not be achieved even with a vast amount of experimentation and noted that a review of the published literature does not support the information disclosed in the specification of the '216 publication.

The Examiner, however, states that Applicants' arguments are inconsistent with the instant disclosure as filed, opining that Applicants also describe a laundry list of diseases and that Applicants present no working examples to demonstrate administration of follistatin to treat severe acute respiratory distress syndrome or asthma. The Examiner concludes that Applicants thus are using a double standard. Applicants respectfully yet strongly disagree with the Examiner's assertion.

First, Applicants submit that the list of conditions described as treatable by the methods of the present invention are:

> septic shock, septicaemia, airway inflammation, appendicitis, meningitis, hepatic response to toxins or viruses, angiogenesis, psoriasis, neural protection, atherosclerosis, renal tubular necrosis, encephalitis, wound healing or traumatic injury such as occurs with injury, surgery and burns (e.g. traumatic brain injury), …asthma, interstitial lung disease, cystic fibrosis, lung transplantation, SARS, bronchiolitis obliterans, emphysema, obstructive pulmonary disease, asbestosis, obstructive sleep apnoea, hypoxia or pulmonary hypertension, …acute systemic inflammatory response [such as] systemic inflammatory response syndrome and even more particularly sepsis, septicaemia, toxic shock, septic shock, tissue trauma, meningitis or appendicitis, … chronic [diseases], …. [such as] multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, psoriasis or wound healing.

the instant application at ¶¶88-93. These conditions and diseases are repeated more or less verbatim at paragraphs [0079] - [0083], [0107]- [0111], [0172] – [0176], [0191] – [0195], and [0211] – [0215], and present a far more limited "laundry list" than that disclosed in the '216 reference. Further, the list of conditions described as treatable by the methods of the present invention are confined to those conditions that have an inflammatory component in their progression--as opposed to the diverse list of diseases listed in the '216 publication--such that one of skill in the art could interpolate the teachings in the current application and apply them to a particular condition in those listed. It should also be noted that several of these conditions, such as septicemia and asthma, are actually the subject of one or more of the examples exemplified in the current application.

The Examiner has alleged that the instant specification does not contain working examples to demonstrate enablement comprising the administration of follistatin to treat severe acute respiratory syndrome or asthma to mice or humans. Applicants submit that the instant application **does** provide working examples, unlike the '216 publication. For instance, Example 2 teaches assessment of activin and follistatin in a mouse model of experimental allergic asthma; Example 3 expands the teaching to include characterization of activin, activin receptor and follistatin mRNA expression in this mouse model of asthma along with the immunohistochemical localization of these proteins in patient samples from cystic fibrosis or asthmatic patients; Example 4 teaches the importance of the relationship between pulmonary expression of activin and follistatin in acute pulmonary inflammation; Example 5 teaches the expression of activin and follistatin in airway remodeling, a consequence of acute airways inflammation; and Example 6 teaches methods for using follistatin treatment to prevent pulmonary inflammation and enhancing resolution in a mouse asthma model. More particularly, the instant application presents methods that address mouse asthma models and human clinical conditions such as asthma, stating that follistatin treatment is beneficial.

Specifically, the description and methods of Example 6 refer to follistatin treatment and the blockade of activin, specifically mentioning follistatin treatment, reciting, "These data provide information regarding the ability of activin neutralization to ameliorate allergic pulmonary inflammation" (specification at ¶240). In addition, the instant specification describes how mice in the asthma model are treated with follistatin stating, "these data provide information regarding the ability of follistatin to inhibit the airway remodeling response" (specification at ¶241). Details of the dose of administration, route of administration, frequency of administration and method of detecting attenuation of pulmonary inflammation are all given (specification at ¶240-1). Applicants further point out that the example demonstrating the ability of follistatin to attenuate the allergic inflammatory response in mice uses a widely-accepted model of clinical asthma based on sensitivity to the allergen, ovalbumin.

The work described in Examples 2-6 of the instant application was subsequently published by Applicants in an international journal (see Hardy *et al.*, *Clin Exp Allergy*, 36:941-50 (2006), provided herewith as **Exhibit A**), after review by external referees and a journal editor. Furthermore, the teaching of Example 6--specifically that follistatin can be used to treat acute allergic asthma in a mouse model--is confirmed in the results described on p. 947 of Hardy

et al. (2006) and in Figure 7, showing that follistatin treatment reduces the number of inflammatory cells in draining lymph nodes and the number of respiratory cells indicative of remodeling in the basement epithelium of airways. Further exploration of this teaching was published internationally by Applicants in Hardy *et al., Am. J. Respir. Cell Mol. Biol.* 42:667-75 (2010), provided herewith as **Exhibit B**). On p. 675 of Hardy *et al.* (2010), the authors state, 'Together, these findings underscore the idea that, along with TGF-β, activin A plays an important role in asthma pathogenesis and suggest that targeting this pathway holds therapeutic potential.' Based on the teaching in the instant application, one of skill in the art would know that targeting the activin pathway for therapeutic potential would involve administration of follistatin, which could also be extrapolated to other acute inflammatory airways conditions such as severe acute respiratory distress syndrome.

Applicants also point out that the use of lipopolysaccharide (LPS) in several of the other examples in the instant disclosure, specifically Examples 1, 7 and 9, teaches that follistatin can bind to activin and block the biological actions of activin released in response to LPS. This is a well-accepted model of acute inflammation involving multiple organ pathology including the lung. If the LPS is administered by pulmonary inhalation, LPS can also be used to induce airways inflammation (He *et al.*, *Respir Res*, 10:126 (2009) , provided herewith as **Exhibit C**). As such, the ability of follistatin to block activin A released by LPS is a representative model of acute respiratory distress syndrome.

Thus, Applicants contend that the '216 publication is not an enabling disclosure, the de Kretser Declaration supports Applicants' position in this regard, the instant specification does provide working examples, and that the Applicants are not using a double standard. Applicants thus request that the rejection of claims 74-75 and 78 under 35 U.S.C. §102(b) as allegedly being anticipated by the '216 publication be withdrawn.

The Examiner has rejected claims 74-78 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Publication 2003/0162715 (hereinafter "the '715 publication"). The '715 publication allegedly discloses follistatin-like-3 protein to treat disease, and mentions many therapeutic indications treatable by administration of follistatin-like-3 protein. Although the Examiner agreed with Applicants that follistatin-3 is different from follistatin, the Examiner states that

those with skill in the art would have had reason to use the follistatin of the instant application as a substitute for the treatment taught in the '715 publication because, like follistatin-3 taught in the '715 publication, follistatins are activin antagonists. The Examiner argues further that substituting a known element for another to yield a known result is obvious (citing *KSR*, 550 U.S. 416, 421 (2007)).

Applicants again assert that follistatin-3 (also known as follistatin related-gene or FLRG) and follistatin are not substitutions for one another. Even the '715 reference states, "we demonstrate that FLRG is a functional activin-binding protein which, like follistatin, binds both activin A and activin B... [h]owever, we demonstrate differential expression in tissues and regulation of follistatin and FLRG expression in cultured keratinocytes... [o]ur results indicate differences in the *in vivo* regulation and functions of FLRG and follistatin proteins" (the '715 publication at ¶549). Moreover, when describing the scope of the invention in relation to follistatin-3, the '715 publication states in ¶¶0015-0017:

> [one enablement of the invention comprises] the amino acid sequence of the full-length follistatin-3 polypeptide having the complete amino acid sequence shown in SEQ ID NO:2 (i.e., positions -26 to 237 of SEQ ID NO:2); (b) the amino acid sequence of the full-length follistatin-3 polypeptide having the complete amino acid sequence shown in SEQ ID NO:2 excepting the N-terminal methionine (i.e., positions -25 to 237 of SEQ ID NO:2); (c) the amino acid sequence of the predicted mature follistatin-3 polypeptide having the amino acid sequence at positions 1 to 237 in SEQ ID NO:2; (d) the amino acid sequence of the full-length follistatin-3 polypeptide having the complete amino acid sequence encoded by the cDNA clone contained in ATCC.RTM. Deposit No. 209199; (e) the amino acid sequence of the full-length follistatin-3 polypeptide having the complete amino acid sequence excepting the N-terminal methionine encoded by the cDNA clone contained in ATCC.RTM. Deposit No. 209199; and (f) the amino acid sequence of the mature follistatin-3 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC.RTM. Deposit No. 209199. The polypeptides of the present invention also include polypeptides having an amino acid sequence at least 80% identical, more preferably at least 90% identical, and still more preferably 95%, 96%, 97%, 98% or 99% identical to those described in (a), (b), (c), (d), (e) or (f) above, as well as polypeptides having an amino acid sequence with at least 90% similarity, and more preferably at least 95% similarity, to those above.
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> An additional embodiment of this aspect of the invention relates to a peptide or polypeptide which comprises the amino acid sequence of an epitope-bearing portion of a follistatin-3 polypeptide having an amino acid sequence described in (a), (b), (c), (d), (e) or (f) above. Peptides or polypeptides having the amino acid sequence of an epitope-bearing portion of a follistatin-3 polypeptide of the invention include portions of such polypeptides with at least six or seven, preferably at least nine, and more preferably at least about 30 amino acids to about 50 amino acids, although epitope-bearing

> polypeptides of any length up to and including the entire amino acid sequence of a polypeptide of the invention described above also are included in the invention.
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> A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a follistatin-3 polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of a follistatin-3 polypeptide, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

Since follistatin share only 43.25% amino acid sequence homology with follistatin-3, follistatin would not fall within what is taught by the ‘715 publication, nor would it be suggested by the ‘715 publication.

The Examiner agrees that follistatin and follistatin-3 are different, but contends that follistatin and follistatin-3 are taught in the ‘715 publication as both being activin antagonists and states further that substituting a known element for another to yield a known result is obvious (citing *KSR*, 550 U.S. 416, 421 (2007)). The Applicants respectively contend that this substitution is largely at a biochemical level and that one of skill in the art would know that studies comparing follistatin-3 and follistatin do not support substituting follistatin-3 for follistatin in a biological context.

The Examiner is referred to the findings of Sidis *et al.*, *Endocrinology*, 143:1613-24 (2002), provided herewith as **Exhibit D** (and provided as Exhibit J with the de Kretser Declaration). This publication contrasts the effectiveness of follistatin-3 (termed FSRP in this publication) with follistatin in terms of activin antagonism in a number of settings that have differing relevance to clinical or therapeutic benefit. On p. 1616, the authors use a radioligand binding assay to demonstrate that follistatin has ~2.4-fold higher affinity for activin in terms of biochemical binding than follistatin-3, which confirmed their previous estimate (Tortoriello *et al.*, *Endocrinology* 142:3426-34 (2001), provided herewith as **Exhibit E**). A more clinically relevant measure is antagonism of activin by cell monolayers in culture, and Sidis and colleagues demonstrate on p. 1617 that in anterior pituitary cell monolayers follistatin is ~50-fold more effective than follistatin-3 in blocking activin activity. On p. 1618, these authors provide an even more clinically relevant measure of activin antagonism, where in primary pituitary cell cultures follistatin is ~100-fold more effective than follistatin-3 in blocking activin activity. Applicants

point out that follistatin-3's ability as an activin antagonist therefore diminishes significantly from biochemical binding through to cell monolayer cultures *in* vitro and still further in primary cell cultures *in vitro*. It should also be noted that an *in vivo* or therapeutic demonstration of follistatin-3 antagonism has not been published to date and one of skill in the art would not contemplate such a demonstration given the teachings of Sidis *et al.* showing that follistatin-3 is an ineffective antagonist of activin in anything other than in a strictly biochemical setting.

The Examiner argues quite correctly that follistatin-3 can bind activin A and activin B as shown in the '715 publication. However, it is important to note that this finding addresses molecular interactions in a biochemical setting. The Applicants do not contest that follistatin-3 can bind activin A and activin B by such techniques, but wish to point out that this does not demonstrate or teach that follistatin-3 can antagonize the actions of activin in either an *in vitro* or an *in vivo* setting. This supposition is clearly supported by Figure 4 from Sidis et al. (2002, p. 1618), where the capacity of follistatin-3 as an activin antagonist decreases dramatically in an *in vitro* setting compared with a biochemical action, and as stated above.

If anything, the Sidis *et al.* (2002) publication teaches that an activin antagonist function for follistatin-3 is not to be expected apart from a biochemical setting where flag-tagged follistatin-3 was used to bind activin and the complex was then immunoprecipitated using a flag-tagged antibody, as demonstrated in the '715 publication. This is quite different to follistatin-3 being used in an *in vitro* or *in vivo* biological setting. Furthermore, in a follow-up study published by the group (Sidis et al., *Endocrinology*, 147:3586-97 (2006) (provided herewith as **Exhibit F**), the authors show that if a mutant follistatin-3 was expressed as a membrane-anchored protein, its capacity to block activin was dramatically increased (Figure 6A and p. 3592), again emphasizing the importance of the capacity to bind and anchor an activin-follistatin complex to cell surfaces for effective neutralization and degradation.

The point that the Applicants wish to stress is that follistatin-3, because of its structure, is fundamentally different to follistatin in that it cannot bind to cell surfaces as it lacks the heparin binding site and affinity for heparin sulfate proteoglycans, as shown in Figure 1 from the publication of Stamler et al., *J. Biol. Chem.*, 283:32831-8 (2008), provided herewith as **Exhibit G**. Follistatin has a lysine-rich heparin binding sequence in the follistatin domain 1, which enables follistatin to bind to heparin sulfate proteoglycans on cell surfaces, targeting any follistatin-bound activin to a lysosomal degradation pathway. Follistatin-3 has no such site and

cannot initiate the degradation of activin after it is bound, making it ineffective in modulating the bioactivity of activin A or activin B in the whole animal, that is, *in vivo*. The property of heparin binding is resident in both FS288 and FS315, although in the latter isoform it cannot bind to cell surfaces until it has bound activin, as the extra amino acids in FS315 normally mask the heparin binding site. Either isoform of follistatin can bind to activin, the complex is bound through the heparin binding site to cell surfaces, is internalized so that activin **cannot** dissociate and circulate again, and is destroyed by being degraded by lysosomes. Applicants again contend that this mechanism is a potent clearance pathway to limit the actions of activin and emphasize that follistatin-3 does not have this heparin binding site in its structure, therefore cannot neutralize activin through this degradation pathway and consequently has **not** been shown in any biological setting to be an effective activin antagonist.

In his Declaration, Dr. de Kretser concludes that because inflammatory disorders involve the production of endogenous activin at one or more sites, the absence of the heparin binding site in follistatin-3 would render it ineffective as a therapeutic in the context of inflammation. As one of skill in the art would appreciate, inflammation almost always occurs at an **extracellular** level within a tissue, within a number of organs, such as the lungs, or systemically throughout the body. Follistatin-3 has been shown to have a predominantly **intracellular** localization as demonstrated by Tortoriello *et al.*, **Exhibit E**). On p. 3431, these authors state, 'FSRP [follistatin-3] immunoreactivity was detected in all cells examined. However, rather than showing a cytoplasmic or endoplasmic reticular/Golgi pattern commonly observed for secreted proteins such as FS, in all cases FSRP immunoreactivity was predominantly confined to the nucleus (Fig. 6, A–C).' Applicants again contend that the heparin binding site is critical to follistatin's capacity to act as an *in vivo* antagonist of activin. For instance, it can block the biological actions of the activin released in response to an inflammatory challenge such as LPS, as shown in a subsequent publication by the Applicants where follistatin can block the effects of a lethal dose of LPS (Jones *et al.*, *Proc Natl Acad Sci USA*, 104:16239-16244 (2007), provided herewith as **Exhibit H**). Again as stated previously, the latter is a well-accepted model of clinical septicemia where multiple organ pathology including the lung is involved, and if the LPS is administered by pulmonary inhalation, can be used to induce airways inflammation (again see He *et al.*, **Exhibit C**). As such, the ability of follistatin to block activin A released by LPS is a representative model of acute respiratory distress syndrome.

Additionally, as with the ‘216 publication, the ‘715 publication fails to exemplify even one therapeutic indication that can be treated with follistatin-3. Nevertheless, the ‘715 publication recites that follistatin-3 may be useful in the treatment of:

> Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.
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> Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.
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> Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.
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> Similarly, follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, may also be used to modulate inflammation. For example, follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)….
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> Examples of hyperproliferative disorders that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but are not limited to neoplasms located in the: abdomen, bone, breast,

digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects….

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis….

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency….

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis….

Ocular disorders associated with neovascularization which can be treated with the follistatin-3 polynucleotides and polypeptides of the present invention (including follistatin-3 agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization.

Moreover, disorders and/or states, which can be treated with be treated with the follistatin-3 polynucleotides and polypeptides of the present invention (including follistatin-3 agonist and/or antagonists) include, but are not limited to, solid tumors,

blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubcosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by follistatin-3 polynucleotides or polypeptides, as well as antagonists or agonists of follistatin-3, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, follistatin-3 polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma,

lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by follistatin-3 polynucleotides or polypeptides, as well as agonists or antagonists of follistatin-3, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia….

[F]ollistatin-3 polynucleotides or polypeptides, as well as agonists or antagonists of follistatin-3, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associted with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Follistatin-3 polynucleotides or polypeptides, as well as agonists or antagonists of follistatin-3, could be used to promote dermal reestablishment subsequent to dermal loss….

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza),

Papovaviridae, Parvoviridae, Picornaviridae, Poxyiridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease,

> opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. Follistatin-3 polynucleotides or polypeptides, or agonists or antagonists of follistatin-3, can be used to treat or detect any of these symptoms or diseases.

'715 publication at ¶¶392-440. As argued in relation to the '216 publication, Applicants contend that "tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Applicants submit that the '715 publication like the '216 publication simply tosses out the mere germ of an idea to use follistatin-3 to treat a voluminous array of human diseases and disorders (essentially every disease or disorder known to mankind) without one single example or exemplification of success using follistatin-3 to do so, nor has one single example of exemplification of success for treatment of human diseases been published in the international scientific literature subsequent to the '715 publication. Applicants respectfully submit that one skilled in the art would have had to perform an undue amount of experimentation to decipher which, if any, of the therapeutic indications recited in the '715 publication are indeed treatable by follistatin-3--much less any perceived substitutes for follistatin-3--particularly given the unpredictable nature of the biological arts and the biological differences between follistatin and follistatin-3.

Because follistatin and follistatin-3 are not substitutes for one another--particularly in the context of activin binding in any setting other than a biochemical setting and certainly not *in vivo*--and because the '715 publication like the '216 publication simply tosses out the mere germ of an idea to use follistatin-3 to treat an array of human diseases and disorders, Applicants request that the rejection of the claims under 35 U.S.C. §103(a) as allegedly being obvious in light of the '715 publication be withdrawn.

Claims 74-78 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Publication 2002/0192216 or WO 8911862 (hereinafter "the '862 publication"), each in view of WO 03/006006057. The Examiner reiterates his arguments regarding the '216 publication and states that the '216 publication differs from the claimed invention in the recitation of follistatin 288 or follistatin 315 in claims 76-77, but the '057 publication teaches a single chain follistatin molecule comprising 288 and 315 amino acids. Again, the Examiner argues that substituting a

known element for another to yield a known result is obvious (citing *KSR*, 550 U.S. 416 at 421); and again, Applicants submit their arguments in relation to the '216 publication, above, none of which are overcome by the addition of the '057 publication.

As for the '862 publication, Applicants argue that the '862 publication teaches inhibin, and combining the '862 publication with the '057 publication teaching use of follistatin (whether generally or the two specific isoforms) does not teach the present invention. Again, follistatin and inhibin are completely different molecules and there would be no motivation for one with skill in the art to combine these references. First, as stated in the de Kretser Declaration filed 08 July 2011 at ¶17, inhibin and follistatin are different proteins arising from unlinked genes located on separate chromosomes, and comprise very different molecular structures. Inhibin is a member of the transforming growth factor-β (TGF-β) superfamily, and is a dimer consisting of an α-subunit crosslinked to a β-subunit (either βA or βB subunits, which are shared with activin), whereas follistatin is a single-chain polypeptide with three follistatin domains. Second, knock-out models of follistatin result in a neonatal lethal with offspring demonstrating defective diaphragms, skeletal defects and growth retardation. Knock-out models of inhibin, on the other hand, are born alive and at 3-4 weeks of age develop gonadal and adrenal tumors and cachexia and die shortly thereafter. Third, as described in the de Kretser Declaration at ¶18, inhibin and follistatin compete with activin at different cellular levels such that the impact of inhibin and follistatin on activin are fundamentally different--the former being a receptor competitor and the latter being a high affinity binding protein. Most importantly, inhibin may act as an activin anatagonist in some settings but not in others, whereas follistatin invariably antagonizes and blocks activin actions. Also, as noted by Dr. de Kretser at ¶19, the only noted effect of inhibin when given *in vivo* and exogenously is to inhibit the reproductive hormone follicle-stimulating hormone; there is no information in the public domain illustrating that inhibin can be administered *in vivo* to effectively any modulate inflammatory process.

Thus, Applicants submit that the teachings of the '862 publication are confusing, have not been substantiated by research in the years since the filing of the application that led to the '862 publication, would not lead one skilled in the art to combine these references, nor would such a combination arrive at the present invention. Additionally, as Dr. de Kretser points out at ¶20 of his Declaration, statements in the '862 publication have been refuted insofar as it discloses that activin is suitable for inhibiting transplantation rejection responses. The utility of

activins for inhibiting transplantation rejection is not supported by the literature, which instead teaches that an activin antagonist—follistatin—actually is beneficial in transplantation responses.

Therefore, Applicants assert that the standard from *KSR* that it is obvious to substitute a known element for another to yield a known result does not apply in the context of inhibin and follistatin, and respectfully request that the rejection of the claims under 35 U.S.C. §103(a) as allegedly being unpatentable over the '862 publication be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the subject application--with pending claims 74-78--is in condition for allowance, which action is earnestly solicited. Should the Examiner have any questions, please contact the undersigned at any time at the phone number listed below.

Respectfully submitted,

/Sarah Brashears/

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